

PATENT COOPERATION TREATY

PCT

Plougmann & Vingto

INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Article 36 and Rule 70)

24 JAN. 200

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| Applicant's or agent's file reference P34546PC01 | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA416) | |
| International application No. PCT/DK 03/00794 | International filing date (day/month/year) 19.11.2003 | Priority date (day/month/year) 19.11.2002 |
| International Patent Classification (IPC) or both national classification and IPC C12Q1/68 | | |
| Applicant H:S RIGSHOSPITALET et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of ⁸/₉ sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

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|---|---|
| Date of submission of the demand 14.05.2004 | Date of completion of this report 21.01.2005 |
| Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized Officer Costa Roldán, N Telephone No. +49 89 2399-7180  |

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/DK 03/00794

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-43 as originally filed

Sequence listings part of the description, Pages

44-91 as originally filed

Claims, Numbers

1-41 as originally filed

Drawings, Sheets

1-13 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
☒ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

**INTERNATIONAL PRELIMINARY
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International application No. PCT/DK 03/00794

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 16-25,31-34

because:

☒ the said international application, or the said claims Nos. 31-34 (IA) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 16-25

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|-------------|------------------|
| Novelty (N) | Yes: Claims | 1-15,26-41 |
| | No: Claims | |
| Inventive step (IS) | Yes: Claims | 1-15,39-41 |
| | No: Claims | 26-38 |
| Industrial applicability (IA) | Yes: Claims | 1-15,26-30,35-41 |
| | No: Claims | |

2. Citations and explanations

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/DK 03/00794**

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 31 to 34 relate to methods of treatment and are therefore considered by this Authority to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of these claims (see also Art. 34(4)(a)(I) PCT).

Claims for which no International Search Report has been established have not been examined (see Rule 66.1 PCT). Therefore, no opinion is provided with respect to the provisions of Art. 33(1) PCT (i.e. novelty, inventive step and industrial applicability) for **claims 16 to 25**.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1: KRÖBER ET AL: "VH mutation status, CD38 expression level, genomic aberrations, and survival in chronic lymphocytic leukemia" BLOOD, vol. 100, no. 4, (2002-08), pages 1410-16.
- D2: DAMLE ET AL: "B-cell chronic lymphocytic leukemia cells express a surface membrane phenotype of activated, antigen-experienced B lymphocytes" BLOOD, vol. 99, no. 11, June 2002, pages 4087-93.
- D3: WO-A-0044788

V. 1. NOVELTY (Article 33(1) and (2) PCT)

The prior art is silent as to the following:

* methods for establishing a diagnosis of a subtype of B-cell chronic lymphocytic leukaemia (B-CLL) and methods for establishing prognosis of B-CLL comprising, detecting the presence or absence of one expression product comprising a nucleotide sequence selected from the group of SEQ ID NOS: 12 to 18 (novel), and methods for

determining whether an individual has B-CLL sub-type with poor prognosis by determining the level of expression product of SEQ ID NOS: 12 to 18 (claims 1-15),
* a polynucleotide encoding the polypeptide with amino acid sequence with SEQ ID NO: 3 having interleukin or cytokine activity, and the use of said polypeptide (claims 26-33),
* a method for producing an antibody with specificity against polypeptide with amino acid sequence with SEQ ID NO: 3 and an antibody obtained by said method (claims 35-36),
* a polynucleotide sequence with SEQ ID NO: 5 comprising the nucleotide sequence selected from the group consisting of SEQ ID NO: 2, 4, 6, 7, 8, 9, 10, 11 (claims 37-38)
* kits comprising a detector molecule and at least one of the expression products with SEQ ID NOS: 12 to 18 (claims 39-41),

The subject-matter of **claims 1 to 15, 25 to 41** is therefore new (Art. 33(2) PCT).

V.2. INVENTIVE STEP (Article 33 (1) and (3) PCT)

V.2.1. Inventive step for claims 1 to 15, 39-41:

D1 relates to chronic lymphocytic leukemia (CLL), and studies biologic risk factors such as immunoglobulin variable heavy chain gene (V(H)) mutation status (by e.g. PCR), CD38 expression level, and genomic aberrations (by FISH) for prognostic values. It mentions that through univariate statistical analyses, unmutated V(H) genes and high CD38 expression levels predicted for shorter survival times.

Document D1 is regarded as being the closest prior art to the subject-matter of claim 1.

The subject-matter of claim 1 differs from this known D1 in that it mentions sequences with SEQ ID NOS: 12 to 18.

The problem to be solved by the present invention may be regarded as an alternative method for establishing a diagnosis of a subtype of B-CLL leukaemia.

The solution to this problem proposed in claim 1 of the present application is the use of nucleotide sequences SEQ ID NOS: 12 to 18.

The prior art (see e.g. Abstracts of D1 or D2) describes the overexpression and/or underexpression of genetic markers in cell from B-CLL patients. D1, however, is silent as to nucleotide sequences with SEQ ID NOS: 12 to 18.

Therefore, in view of the fact that the prior art (D1 alone or in combination with the available prior art) does not provide any hint that would lead the person skilled in the art to arrive to nucleotide sequences with SEQ ID NOS: 12 to 18 and to use them for establishing a diagnosis of a subtype of B-CLL, independent **claim 1** is considered inventive and thus in compliance with Article 33(3) PCT.

D1 or any of the available prior art, does not mention methods for establishing prognosis and methods for determining whether an individual has B-CLL sub-type with poor prognosis by determining the level of expression product of SEQ ID NOS: 12 to 18. Therefore, subject-matter of independent **claims 2 and 3** is considered as involving an inventive step (Article 33(3) PCT). Dependent **claims 4 to 15** as such also meet the requirements of the PCT with respect to novelty and inventive step.

The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding independent **claim 39** (relating to a kit comprising nucleotide sequences with SEQ ID NOS: 12 to 18) and dependent **claims 40 and 41**, which therefore are considered new and inventive.

V.2.2. Inventive step for claims 26 to 34, 37 and 38:

Claims 26 and 37 relate to polypeptide and polynucleotide sequences for which novelty has been acknowledged (see above). The claimed sequences are not functionally limited. Furthermore, the description reveals these sequences to be nothing more than expressed sequence tags (see page 6). This Authority considers that the provision of sequences per-se without functional limitation is merely arbitrary and routine matter given the techniques available for the skilled person at the time of filing.

In addition, although claim 27 refers to a function, namely having Interleukin or Cytokine activity, this Authority considers that there is no evidence in the disclosure of the present application to substantiate this claim. The only tentative evidence which remotely indicates function is in page 17, wherein it is stated that "The 3D structure of the protein is very similar to 4-helical cytokines and in particular IL4". This Authority is of the opinion that mere 3D structural similarities is in not a reliable way to assign biological function, thus there is a doubt as to the credibility of the function of said sequence. As a consequence, until the applicant can provide further substantiating data, inventive step can not be recognized.

Therefore, **claims 26 to 28, 37 and 38** are not considered inventive as is the

requirement of Article 33(3)PCT.

The same reasoning applies, *mutatis mutandis*, to the subject-matter of the corresponding independent **claims 29, 31 and 32 and dependent claims 30, 33 and 34** (pertaining to their use) which therefore are considered not inventive.

The same reasoning applies, *mutatis mutandis*, to the subject-matter of the corresponding independent **claim 35** (pertaining to methods of producing antibodies, very well-known for the person skilled in the art, see e.g. D3, claim 1) **and independent claim 36** (pertaining to the product) which therefore are considered not inventive.

V.2.2. Summarizing claims 1 to 15, 39 to 41 meet the requirements of the PCT with respect to novelty and inventive step.

FURTHER COMMENTS:

A. Certain defects in the International Application:

- * Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D3 is not mentioned in the description, nor are these documents identified therein.

- * Article 6 PCT:

- a) claims comprising the term "stringent conditions" lack clarity, because said term is vague and imprecise (Article 6 PCT),

- b) step I) of claim 35 relates to "providing a host organism", and thus encompass human beings. It should be amended by including the term non-humans.

- * It is not possible to incorporate the teaching of a prior art document into the present application's disclosure by the expression "incorporated by reference" (see p. 1, I. 3-4) (cf. PCT Guidelines, C-II, 4.17).

- * First step of method claim 35 relates to "providing a host organism". It is drawn to the Applicant's attention that in the case that the application enters the regional phase an objection under morality could be raised, because humans are encompassed in said step.